P990035

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Ultrasound Bone Sonometer
Device Trade Name:	The Sunlight Omnisense™ Ultrasound Bone Sonometer
Applicant's Name and Address:	Sunlight Ultrasound Technologies Ltd. Weitzmann Science Park Building #3 P.O. Box 2513 Rehovot 76100 ISRAEL
Applicant's U.S. Representative:	Jonathan S. Kahan, Esq. Hogan & Hartson L.L.P. Columbia Square 555 Thirteenth Street, N.W. Washington, D.C. 20004-1109
PMA Number:	P990035
Date of Notice of Approval to the Applicant:	January 20, 2000

II. INDICATIONS FOR USE

The Sunlight Omnisense™ (Omnisense) Ultrasound Bone Sonometer is a non-invasive device that is designed for the quantitative measurement of the velocity of ultrasound waves ("Speed of Sound" or "SOS in m/sec") propagating along the distal one-third of the radius bone. SOS provides a measure of skeletal fragility. The output is also expressed as a T-score and Z-score and can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and other medical conditions leading to reduced bone strength and, ultimately, in the determination of fracture risk.

The SOS measured by Omnisense has a precision error low enough in comparison with the expected annual change in a patient's measurement to make it suitable for monitoring bone changes which occur in the early years following menopause (i.e., age range approximately 50-65 years).

III. CONTRAINDICATIONS

None Known.

IV. WARNINGS AND PRECAUTIONS

Warnings:

Never attempt to operate the Omnisense unit if it is plugged into an outlet that does not meet all electrical code requirements.

Make sure that there is proper grounding in the wall outlet.

The Omnisense is not suitable for use in the presence of a flammable anesthetic mixture containing air, oxygen or nitrous oxide.

Always shut down the system using the switch at the rear panel before plugging or unplugging the Main unit.

Precautions:

The Omnisense probe should not be used on subjects with breached skin or open sores on the skin area that comes with contact with the probe.

Use the Omnisense only indoors, in a clean, dry environment.

To prevent fire or electric shock, do not open or expose the Omnisense Main Unit to rain or moisture.

Do not operate or store the Omnisense near a heat source or air conditioner and always store the System Quality Verification (SQV) phantom near the Omnisense Main Unit.

The system is not sterile. Thus, the probe must be cleaned and disinfected before each patient session. The correct cleaning and disinfection procedure is described in the Omnisense User Guide, "Cleaning and Disinfecting the Omnisense", in Chapter 11.

The Omnisense provides no protection against the harmful ingress (entry) of liquids. Hence, when cleaning the unit, avoid applying liquid near probe connections and the sockets.

SQV phantom and probes should not be immersed in liquid of any kind. Alcohol-free, dry or pre-moistened wipes may be used to clean them.

Use Sunlight recommended and approved ultrasound coupling gels with the Omnisense sonometer to generate and maintain acoustical contact of the probe with the skin.

Sunlight ultrasound gel is for external use only.

When applying ultrasound coupling gel, do not use a Q-tip, an examination glove treated with talc, or any other applicator that may introduce fibers or other foreign matter into the probe.

Do not expose the SQV phantom and the monitor screen to direct sunlight.

When conducting the System Quality Verification procedure, avoid touching the temperature indication strip on the phantom with the fingers, as this affects the phantom temperature reading required for correct interpretation of the procedure results.

When conducting System Quality Verification, be sure that no air bubbles are trapped in the gel between the phantom and probe, as this affects the acoustic contact of the probe with the phantom.

Refer all service problems to qualified Sunlight representative only.

Monitors, printers and other interfacing accessories used with the Omnisense bone sonometer must meet IEC 601-1, IEC 950, UL 2601 or equivalent safety standards.

V. DEVICE DESCRIPTION

The Sunlight Omnisense™ (Omnisense) Ultrasound Bone Sonometer is a noninvasive PC-based device that employs a hand-held probe designed to measure SOS values. The probe is connected by a cable to the Omnisense Main Unit. During measurement, the probe is applied directly to the skin at the distal one-third of the radius. A thin layer of Sunlight Ultrasound Gel is applied between the probe surface and the skin to facilitate good acoustic coupling. Inaudible high frequency acoustic waves, at a center frequency of

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1.25MHz, are produced by two transducers (called ultrasound signal generators or transmitters) in the probe. The ultrasound waves are conducted along the bone and then detected by two different transducers (called ultrasound signal detectors or receivers) in the same probe.

The device's software compares the SOS result with the SOS of a young healthy population, as well as an age-matched population, using an embedded reference database ("normative database"), and reports the comparison in the form of a T-score and a Z-score. A T-score is the difference between the measured SOS value of the subject, and that of the average value of the young healthy population, described in units of standard deviation (SD) of the young healthy population. A Z-score is defined as the difference between a patient's SOS result and the mean SOS of the age and gender-matched normal population, given also in units of standard deviation of the population. Thus, if a patient has a T-score of -1.5, the patient's SOS is one and one-half SDs below the average SOS of the young healthy population, and if a patient has a Z-score of +0.5, the patient's SOS is one-half SD above the age-matched mean.

A) DEVICE COMPONENTS

The Omnisense is a noninvasive PC-based device that consists of: (1) a desktop personal computer-based Main Unit; (2) a Video Display monitor; (3) a keyboard with integrated trackball; (4) a small hand-held probe; (5) a System Quality Verification phantom; (6) a foot pedal; (7) a positioning gauge; (8) a cushion hand rest; (9) a set of earphones; and (10) a User Guide. The Omnisense is also supplied with a Startup Kit that consists of: (1) three bottles of acoustic contact gel (Sunlight Ultrasound Gel); (2) a 100 MB high capacity Zip™ diskette; (3) a 1.44 MB floppy diskette; (4) a skin marker pencil; (5) a screw driver; and (6) two replacement line power fuses.

The user interface with the Omnisense is comprised of the keyboard and the integrated trackball, the video display monitor, the foot-pedal and an optional printer (which is not supplied with the Omnisense). The operator uses these accessories mainly to input patient information into the PC. These accessories are also used for entering other administrative input required in order to operate the system, such as operator's I.D. and password, or the names of new operators or physicians. The software displays to the operator the list of previously measured patients, enables the user to edit a patient information record, and follows the progress of the measurement procedure.

An off-the-shelf printer may be used to generate a record of the patient information entered and the SOS Measurement Result, as well as the corresponding T-scores and Z-scores. The printer may also be used to print Patient History data and SQV History data.

The System Quality Verification (SQV) procedure and a phantom, which is supplied with the system, are used to verify that the entire system is working properly. The phantom, which is designed to be a substitute for bone, is composed of a homogenous hard polymeric material that transmits ultrasound signals at known speeds of approximately 2750 m/sec at room temperature. As a daily routine, the operator is requested to perform the SQV procedure. The SQV measurement procedure is performed in a manner similar to the measurement of the SOS of the radius and the same equations are used to compute the SOS value.

Two aids are supplied with Omnisense: a radius measurement gauge, and a hand rest. The gauge is made of a spring-loaded measuring band, connected at one end to a flat platform. The operator then uses the gauge to measure the distance from the elbow to the tip of the third finger. Using a skin marker, which is provided with the Starter Kit, a mark is drawn around the forearm at exactly the mid-point from the elbow to the third finger tip, which is the distal border of the Region of Interest.

Other accessories provided with Omnisense include a set of earphones for listening to the On-Line Measurement Methodologies, and a screw driver for tightening the probe connector in its socket. The supplies Starter Kit includes a skin marker, three 250cc bottles of Ultrasound Gel, manufactured for Sunlight by Parker Laboratories, Inc, Orange NJ 07050, one 100MB high capacity Zip™ Disk and one 1.44MB floppy diskette, and two line voltage replacement fuses.

B) DEVICE OPERATION

The procedure for taking measurements with the Omnisense is performed according to the following steps: (1) opening a patient file; (2) marking the measurement position on the limb; (3) preparing the probe and the skin surface; (4) performing the actual bone measurements; and (5) reading and printing the measurement results.

The measurement results are displayed on the monitor. Omnisense reports the bone SOS, together with the T-score and Z-score values, which are computed by the system's software using the patient's measured representative SOS value and the reference database. These values appear, together with a graphical display of the measurement results relative to the normative reference data, on the *Measurement Results* screen. A printout of the results can be obtained if a printer is connected to the Main Unit, and the *Print* button on the screen is pressed. The physician may use these results in conjunction with other clinical risk factors as an aid in the diagnosis of osteoporosis and other medical conditions leading to reduced bone strength and, ultimately, in the determination of fracture risk. In order to monitor bone changes, the physician may recall the record of past measurements (*Measurement History)* on the Video Display monitor or print them out.

Other operations can be performed with the help of the graphic user interface of the Omnisense. These include the System Quality Verification (daily procedure to insure proper operability of the Omnisense), database management operations, defining system parameters, and other management operations.

C) PRINCIPLES OF OPERATION

Ultrasound is well established in the medical community as a method, used in its qualitative mode, to obtain in-vivo views of many internal structures. Ultrasound can also be used in a quantitative mode, by measuring various parameters associated with the propagation of a signal through the medium of interest. Quantitative Ultrasound (QUS) is an accepted method for the assessment of bone status, primarily because it offers quick, relatively low cost results without the radiation associated with other traditional techniques such as radiography, x-ray absorptiometry and computed tomography.

Sound energy consists of alternating cycles of compression and rarefaction of the medium through which it is transmitted. Audible sound for humans is in the range of approximately 20 Hz to 20,000 Hz (20 kHz). Ultrasound refers to a range of frequencies that begins at the high-frequency end of the audible range and extends into the Megahertz range.

The propagation of ultrasound through a medium, its speed, its dispersion and the attenuation of signal strength are strongly influenced by the physical properties of that medium. For example, the speed of propagation increases with the density of the medium and its modulus of elasticity (Young's Modulus). Moreover, the microstructure of the medium, as well as macro-structures on the order of a wavelength of the ultrasound, affects the speed. The QUS measure, which is used by the Omnisense, is the *speed of sound transmission* through bone, also known as Speed of Sound (SOS).

The SOS propagation depends, among other factors, on the density of the medium through which it is travelling. At the center frequency used by Omnisense, 1.25MHz, an ultrasound signal travels much faster through the relatively dense, cortical layer of the bone than through the trabecular layer, e.g., approximately 4000 m/s *vs.* 1800 m/s. The signal travels through soft tissue much more slowly than through either type of bone, at a speed of about 1540 m/s.

Sound waves propagate in all directions from the transmitting transducer of the Omnisense probe. Every molecule in the medium acts as a new transmitter, thus propagating the signal again in all directions. Thus, there are many paths that the signal can follow from transmitter to receiver. The Omnisense detects the *first signal to arrive* at the receiving transducer. The time taken by the signal to travel between the transmitter and the receiver is the parameter measured by Omnisense. This propagation time is a function of: (1) the bone SOS; (2) the soft tissue SOS; (3) the average distance between the transducers and the bone; and (4)

the angle of inclination between the surface of the bone and the line connecting the two transducers. The Omnisense software uses a proprietary algorithm to analyze these variables and to calculate the patient's SOS measurement. The device's software then compares the SOS result with the SOS of a young healthy population, as well as an age-matched population, using an embedded reference database ("normative database"), and reports the comparison in the form of a T-score and a Z-score.

VI. ALTERNATIVE PRACTICES/PROCEDURES

A) BONE DENSITOMETRY (BMD)

Different absorptiometric techniques have been established to date as a useful tool for skeletal assessment. Methods of measurement include single energy and dual energy x-ray absorptiometry with x-ray tube sources (SEXA, and DEXA), and spinal and peripheral quantitative x-ray computed tomography (QCT and pQCT). All are capable of evaluating bone mineral density (BMD) as the test parameter. The result is given as an absolute scale, and also relative to population reference values. All of these methods expose the patient and operator to x-ray radiation.

B) BIOCHEMICAL BONE MARKERS

Bone markers estimate the rate of bone resorption and/or bone formation; as such they are considered as an indirect measurement for bone assessment. Nevertheless, they can be used for estimating the rate of change and evaluating response to treatment.

VII. MARKETING HISTORY

Omnisense is being marketed in Israel, the United Kingdom, Italy, Switzerland, Norway, Denmark, Portugal, South Korea, China, Turkey, Egypt, and Brazil, for use at one or more of the following sites: the radius, the metatarsal, and the phalanx. Additionally, Sunlight Ultrasound Technologies Ltd. has authorization to display the CE Marking of Conformity on the Omnisense and the probes accompanied by the KEMA Notified Body Identification number 0344. Omnisense has not been withdrawn from any international market for any reason, including reasons related to safety and/or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH

There are no known potential adverse effects of the Omnisense bone sonometer on a patient's health.

IX. SUMMARY OF PRECLINICAL STUDIES

A) PRECISION

Sunlight conducted two different in vivo precision tests for the Omnisense device. Included in these precision tests were: (1) a reproducibility study which involved the assessment of in vivo precision between different instruments, connecting slot configurations and probes; and (2) a reproducibility study which measured the in vivo precision between different operators and probes.

The objectives of both studies were to estimate the variability, between device components and between operators, of SOS measurements of the distal one-third of the radius. The in vivo precision (reproducibility), expressed by the coefficient of variation (CV), ranged from 0.60% to 0.73%.

B) ACCURACY

Accuracy tests were performed as part of the Omnisense testing to verify compliance with the device's specifications that allow for line voltage variations as well as a range of environmental operating conditions. Two phantoms were measured under different environmental and line voltage conditions while changing the ultrasound probes and probe slot positions. The measured accuracy of the Omnisense was found to comply

with the Omnisense Specification requirement of better than ± 0.2% at both extremes of the SOS measurement range. The CV of the SOS results, computed from five successive measurements, was less than 0.1% in all of the different tests performed using either of the phantoms over a range of environmental conditions and operating line voltages tested.

C) ACOUSTIC OUTPUT TESTING

The Omnisense device was tested to verify compliance of the device with acoustic output limits and requirements in accordance with: (1) the International Standard IEC 61157, "Requirements for declaration of the acoustic output of medical diagnostic ultrasonic equipment" (1993); (2) FDA's 510(k) Guidance: "Measuring and Reporting Acoustic Output of Diagnostic Ultrasound Medical Devices" (1985); and (3) FDA's 510(k) Guidance: "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers" (September 30, 1997). The acoustic output test was performed based on the definitions and methods recognized by the National Electrical Manufacturers Association (NEMA), "Acoustic Output Measurement Standard for Diagnostic Ultrasound Equipment", UD-2 revision 2, NEMA (1997).

The measured acoustic output levels of the Omnisense are summarized below, and are compared well below the limits specified in FDA's Guidance: "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers" (September 30, 1997).

$I_{(SPTA.3)}$ [mW/cm^2]	6.5
$I_{(SPPA.3)}$ [W/cm^2]	3.7
MI	0.24
$W_{(0)}$ [mW]	1.1

D) ELECTRICAL SAFETY

A series of electrical safety tests of the Omnisense was performed to verify the compliance of the Omnisense with the limits and requirements of medical electrical equipment general safety requirements IEC 601-1 (EN 60601-1, 1988), including Amendments 1 (1991) and 2 (1995). The Omnisense device was found to be in conformity with IEC 601-1 (1988) and Amendments 1 and 2.

E) ELECTROMAGNETIC COMPATIBILITY

A series of electromagnetic compatibility tests on the Omnisense was performed and the Omnisense was found to be in compliance with the limits and requirements of the United State Federal Communication Commission (FCC) regulations at 47 C.F.R. Part 15 for radio frequency devices, Subpart B: Unintentional radiators, as well as the requirements of IEC 601-1-2 (EN 60601-1-2), Medical Electrical Equipment - Part 1: General Requirements for Safety, Electromagnetic Compatibility Requirements and Tests, and the associated IEC standards, IEC 801-1 (EN 55011/ANSI C63/4/1992), IEC 801-2, IEC 801-3, IEC 801-4 and 801-5.

F) BIOCOMPATIBILITY

The polyurethane material of the Omnisense probe is the only material that comes into contact with the user and patient. This contact material was tested for biological effects in accordance with Biological Evaluation of Medical Devices - Part 1: Guidance on Selection of Tests First Edition, ANSI/AAMI/ISO-10993-1 that apply to surface devices that contact skin for limited duration (i.e., ≤ 24 hours). For these types of devices, biocompatibility is demonstrated through testing for sensitization, irritation or intracutaneous reactivity, and cytotoxicity. The results from these tests demonstrated that the Omnisense patient contact material meets all applicable biocompatibility requirements.

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G) CLEANING AND DISINFECTION

The Omnisense ultrasound probe is considered a non-critical, reusable medical device which is applied only to intact skin, and therefore, only low-level disinfection is required. Results from testing to determine the effects of disinfection methods on the probe characteristics demonstrated that a wiping method using Sporicidin Disinfectant Towelettes does not affect the probe parameters and the SOS measurement results and is, therefore, an acceptable method for low-level disinfection procedure. The Omnisense Operator's Manual includes a recommendation that users conduct disinfection procedures of the Omnisense probe using Sporicidin Disinfectant Towelettes. These towelettes have FDA 510(k) clearance for disinfection of medical devices (K904579), are EPA registered for "Hospital Disinfection" with AOAC testing protocols (Reg. No. 8383-7), and comply with OSHA *Bloodborne pathogen Standard* (29 CFR 1910.1030).

X. SUMMARY OF CLINICAL STUDIES

Five clinical studies were conducted to achieve the following objectives:

- Create normative reference databases of speed of sound ("SOS") in a Caucasian female population. Two clinical studies were conducted, one multicenter study in North America and one single center study in Israel, to collect the necessary information for creating normative databases.

- Assess the ability of the Sunlight Omnisense™ to discriminate osteoporotic fracture subjects from age-matched non-fracture subjects and healthy young subjects, and estimate the risk of osteoporotic fracture. Two studies were conducted to meet this objective; the first study examined only subjects that had hip fractures and a second study enrolled subjects with hip, wrist, or vertebral fractures. A separate analysis also was performed on data pooled from the two studies with respect to the hip fracture subjects.

- Determine the precision of the Sunlight Omnisense™ in a clinical setting. The precision was measured by comparing results obtained from multiple readings taken by different operators on the same subjects to determine whether the SOS measurements are reproducible.

- Evaluate the safety of the Sunlight Omnisense™ Ultrasound Bone Sonometer.

A) NORMATIVE DATABASE STUDIES

1. NORTH AMERICA NORMATIVE DATABASE (STUDY 4205):

Study design and subject population: Study 4205 was conducted in Caucasian females between the ages of 20 and 90 years old by five investigators at five geographically diverse investigational sites in North America (4 in the U.S. and 1 in Canada). Potential subjects were identified by placing advertisements in the newspaper, contacting potential subjects from drivers license listings, recruiting at college and university campuses, and recruiting at nursing homes. Eligible women had a negative history of osteoporotic fracture or chronic conditions affecting bone metabolism, and were not taking medications that affect bone metabolism. Of the 573 subjects recruited, 545 subjects were found eligible according to the inclusion/exclusion criteria of the study and 521 had SOS measurements of the distal one-third radius that were analyzed in this study.

Results: The mean SOS was 4083±146 m/sec with a range of 3532 to 4490. About 90% of the SOS measurements were between 3800 and 4300 m/sec. Over half of the measurements (52%) were between 4000 and 4200 m/sec.

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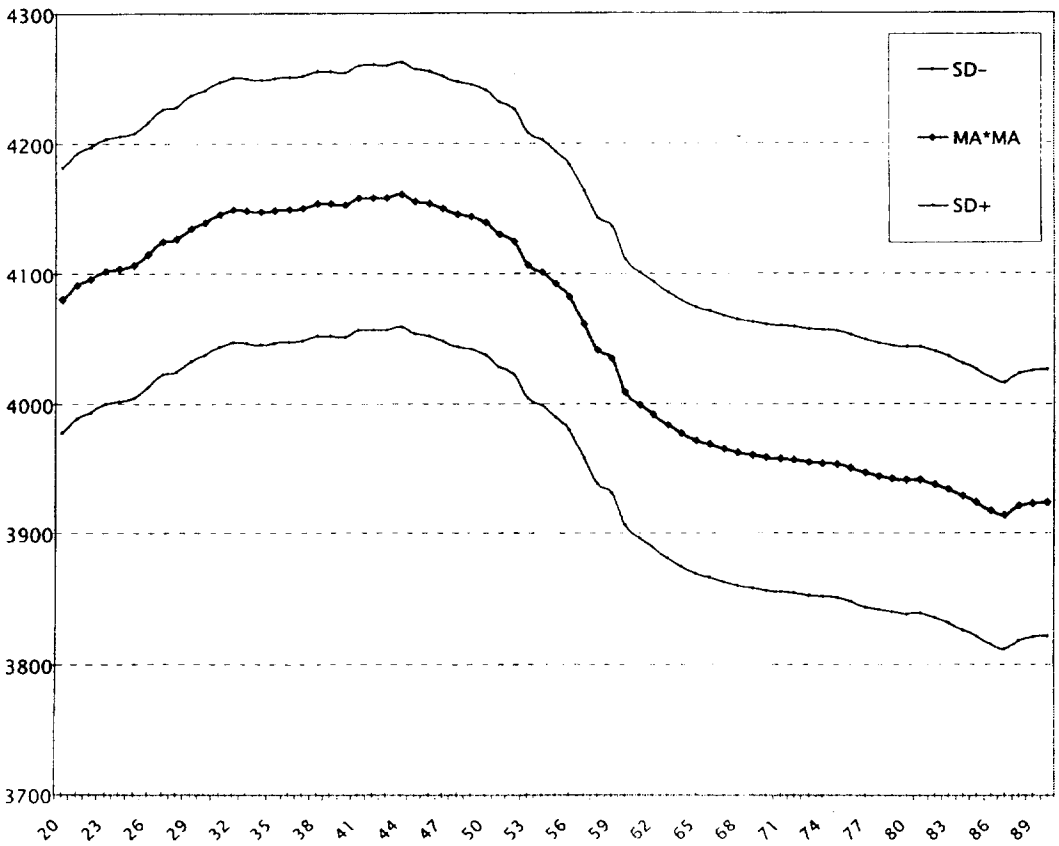
Table 1 presents mean SOS results by age decade. Figure 1 depicts the moving average of the SOS results as a function of age. The moving average SOS increases to a peak of 4158 m/sec at the age of 41, with population standard deviation of 102 m/sec, and declines thereafter. The largest decline, about 15 m/sec/year, is observed around the age of 58, about eight years past the mean age of menopause. At older ages, 65 to 90, the decline slows down to about 2-5 m/sec/year. Linear regression models show that both a straight line and quadratic fit are highly significant ($p<0.0001$).

Table 1: SOS Measurements by Age - Study 4205

Age	Mean±SD
20-29	4103±107
30-39	4150±93
40-49	4161±130
50-59	4095±131
60-69	3971±141
70-79	3949±125
80-90	3921±149
All	**4083±146**

Figure 1: Moving Average SOS by Age - Study 4205



The moving average for the age of 41, and a representative standard deviation taken at the age decade around the peak SOS area, are used to calculate T-scores for each SOS measurement. The mean T-scores by age decade are shown in **Table 2**. The mean T-score of the entire eligible population in the study was -0.75±1.43 with a range of -6.16 to 3.24. Mean T-score reached a low of -2.45 at age 80-89. This table also indicates the percent of subjects in each age decade that had T-scores less than -2.5 (WHO criteria for osteoporosis) and those that had T-score between -2.5 and -1.0 (WHO criteria for osteopenia). Among subjects aged 60-90 years, 35.0% had T-scores less than -2.5 and 42.3% had T-scores between -2.5 and -1.0.

Table 2: SOS T-Scores by Age - Study 4205

Age	N	Mean±SD	T<-2.5 n (%)	-2.5<T<-1.0 n (%)
20-29	92	-0.56±1.05	4 (4.3)	24 (26.1)
30-39	100	-0.10±0.92	1 (1.0)	15 (15.0)
40-49	102	0.01±1.28	2 (2.0)	15 (14.7)
50-59	90	-0.64 ±1.28	7 (7.8)	29 (32.2)
60-69	64	-1.84±1.38	22 (34.4)	24 (37.5)
70-79	48	-2.07±1.23	16 (33.3)	23 (47.9)
80-90	25	-2.34±1.46	10 (40.0)	11 (44.0)
All	**521**	**-0.75±1.43**	**62 (11.9)**	**141 (27.1)**
Range		**-6.16 to 3.24**		

No adverse events of any kind were reported in the course of this clinical study.

Conclusion: The North America normative database for Caucasian female population follows the classical curvature of bone densitometry, with minor variations, since bone properties other than mineral density are probed. The peak SOS value is observed at about the age of 41. A rapid decrease in SOS is further observed on or about the mean age of menopause, 51, reaching a maximal slope of about 15 m/sec/year at the age range of 56 to 62. This change per year should be compared to the measurement precision (see Section 4. below) of about 17 m/sec. Being at about the same value, the Omnisense is shown to have a high sensitivity to change, thus making it suitable for measuring bone status in the first years after menopause when bone changes are most pronounced. At older ages, the change per year moderates to a level of about 2-5 m/sec/year.

The prevalence of osteoporosis (in accordance with the World Health Organization definition) as measured by the SOS in the North American female population at the age of 60-69 was found to be about 35.5% which is comparable to the prevalence observed using axial DXA measurements.

2. ISRAEL NORMATIVE DATABASE (STUDY 205)

Study design and subject population: Study 205 was conducted in Caucasian females between the ages of 20 and 90 years old by a single investigator at Asaff Harophe Medical Center, Zerifin, Israel. The eligibility criteria were met by 1,132 subjects who had their SOS measurements of the distal one-third radius taken.

The mean age of the study subjects was 49.3±17.6 years with a range of 20 to 89 years. Each decade was roughly comparable in size except for the decade 40-49, in which there were 266 subjects. Sixty percent of the subjects in this study were pre-menopausal.

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Results: Table 3 presents mean SOS results by age decade. The mean SOS was 4082±151 m/sec with a range of 3510 to 4602. Ninety percent of the SOS measurements were between 3800 and 4300 m/sec. Over half of the measurements (52.5%) were between 4000 and 4200 m/sec.

The moving average SOS increases to a peak of 4173 m/sec at the age of 39, with population standard deviation of 99 m/sec, and declines thereafter. The largest decline, 15 m/sec/year, is observed around the age of 55, about four years past the mean age of menopause. At older ages, 65 to 90, the decline slows to about 5 m/sec/year. Linear regression models show that both a straight line and quadratic fit are highly significant ($p<0.0001$).

Table 3: SOS Measurements by Age - Study 205

Age	Mean±SD
20-29	4108±95
30-39	4161±101
40-49	4167±98
50-59	4115±128
60-69	3989±151
70-79	3931±129
80-90	3879±159
All	**4082±151**

The mean T-scores by age decade are shown in Table 4. The mean T-score for the study was -0.92±1.53 with a range of -6.70 to 4.33. Mean T-score reached a low of -2.97 at age 80-89. This table also indicates the percent of subjects in each age decade that had T-scores less than -2.5 (WHO criteria for osteoporosis) and those that had T-score between -2.5 and -1.0 (WHO criteria for osteopenia). Among subjects aged 60-90, 44.9% had T-scores less than -2.5 and 34.5% had T-scores between -2.5 and -1.0.

Table 4: SOS T-Scores by Age - Study 205

Age (years)	N	Mean±SD	T<-2.50 n (%)	-2.50<T<-1.0 n (%)
20-29	182	-0.65±0.96	4 (2.2)	60 (33.0)
30-39	185	-0.12±1.02	3 (1.6)	28 (15.1)
40-49	266	-0.06±0.99	2 (0.8)	37 (13.9)
50-59	145	-0.58±1.30	12 (8.3)	34 (23.4)
60-69	160	-1.86±1.53	58 (36.2)	56 (35.0)
70-79	145	-2.44±1.31	68 (46.9)	54 (37.2)
80-90	49	-2.97±1.61	33 (67.3)	12 (24.5)
All	**1132**	**-0.92±1.53**	**180 (15.9)**	**281 (24.8)**
Range		**-6.70 to 4.33**		

No adverse events of any kind were reported in the course of this clinical study.

Conclusions: The Israel normative database for Caucasian female population follows the classical curvature of bone densitometry similar to that of the North America normative database. Peak SOS value is observed at about the age of 39. A rapid decrease in SOS is further observed on or about the mean age of menopause, 51, reaching a maximal slope of

about 15 m/sec/year at the age range of 54 to 57. Similar to the North America case previously described, this change per year may be compared to the measurement precision (see Section 4. below) of about 17 m/sec. Being at about the same value, the Omnisense is again shown to have a high sensitivity to change, thus confirming the findings of the North American study that the Omnisense is suitable for measuring bone status in the first years after menopause when bone changes are most pronounced. At older ages, the change per year moderates to a level of about 5 m/sec/year.

The prevalence of osteoporosis (in accordance with the World Health Organization definition) as measured by the SOS in the Israeli female population at the age of 60-69 was found to be about 32% which is comparable to the prevalence observed using axial DXA measurements.

A) CROSS SECTIONAL STUDIES

1. ASSESSMENT OF HIP FRACTURE RISK (STUDY 201)

Study design and subject population: Study 201 was a cross-sectional case-control study performed at one investigational site in Israel. The objective of this study was to determine the ability of Omnisense SOS measurements to discriminate osteoporotic hip fracture subjects from age matched non-fracture subjects and young healthy subjects, and to determine the fracture risk estimate.

Three different groups of subjects were recruited and analyzed in this study: 50 low trauma hip fracture (HF) subjects, 130 age matched non-fracture subjects (NF) and 185 young healthy subjects (YF). The mean age for the hip fracture group was 76.1±6.0 years with a range of 65 to 85 years. The mean age for the non-fracture group was 71.5±5.2 with a range of 65 to 85 years. The mean age for the young healthy group was 40.6±3.0 with a range of 35 to 45 years.

Results: As seen in Table 5, hip fracture subjects had a mean SOS of 3861±149 m/sec, while non-fracture subjects had a mean SOS of 3966±145 m/sec. The difference between the two groups was statistically significant ($p<0.0001$). Young healthy subjects, on the other hand, had a mean SOS of 4165±96 m/sec, which was greater than the mean SOS of both hip fracture subjects and elderly non-fracture subjects ($p<0.0001$ for both). The SOS distributions for the three study groups are also illustrated in Figure 2. While there is a clear difference in the SOS distributions between the two elderly groups, there is an overlap as well in the range of 3800-3900 m/sec, since it is likely that a significant proportion of the elderly subjects in the non-fracture group might also be osteoporotic.

Table 5: SOS Measurements by Study Group - Study 201

Speed of Sound (m/sec)	Hip Fracture n (%)	Elderly Non-Fracture n (%)	Young Healthy n (%)
<3800	18 (36.0)	15 (11.5)	0 (0.0)
3800-3899	12 (24.0)	32 (24.6)	0 (0.0)
3900-3999	11 (22.0)	35 (26.9)	11 (5.9)
4000-4099	5 (10.0)	22 (16.9)	33 (17.8)
4100-4199	4 (8.0)	19 (14.6)	75 (40.5)
4200-4299	0 (0.0)	6 (4.6)	52 (28.1)
4300+	0 (0.0)	1 (0.8)	14 (7.6)
Total	**50 (100.0)**	**130 (100.0)**	**185 (100.0)**
Mean±SD	**3861±149**	**3966±145**	**4165±96**
Range	**3490 - 4177**	**3582 - 4359**	**3901 - 4407**
T-test p-value (vs. non-fracture)	**<0.0001**	**----**	**<0.0001**
T-test p-value (vs. young healthy)	**<0.0001**	**<0.0001**	**----**

Figure 2: SOS Distribution by Study Group - Study 201

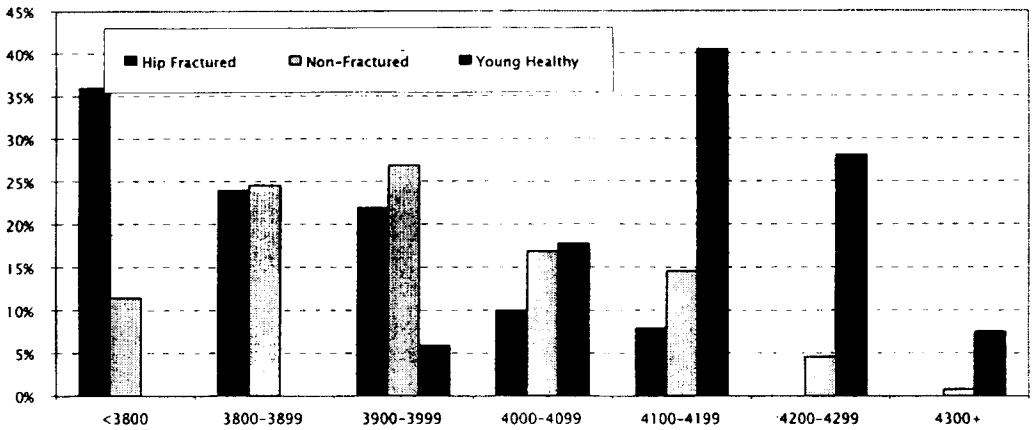

Table 6 shows the distribution of SOS T-scores for hip fracture and non-fracture subjects. Among hip fracture subjects, 70% (35/50) had T-scores less than -2.5, while 39% (51/130) of non-fracture subjects and 1% (2/185) of young healthy subjects had T-scores less than -2.5. Conversely, 10% (5/50) hip fracture subjects had T-scores greater than -1.0, while 24% (31/130) of non-fracture subjects and 85% (158/185) of young healthy subjects had T-scores greater than -1.0.

Table 6: SOS Measurement T-Scores by Study Group - Study 201

T-Score	Hip Fracture n (%)	Elderly Non-Fracture n (%)	Young Healthy n (%)
< -2.5	35 (70.0)	51 (39.2)	2 (1.1)
-2.5 to -1.0	10 (20.0)	48 (36.9)	25 (13.5)
> -1.0	5 (10.0)	31 (23.8)	158 (85.4)
Total	**50 (100.0)**	**130 (100.0)**	**185 (100.0)**
Mean±SD	**-3.11±1.52**	**-2.06±1.47**	**-0.02±0.98**
Range	**-6.91 to 0.10**	**-5.97 to 1.96**	**-2.71 to2.45**

The logistic regression analysis for hip fracture discrimination (*i.e.*, comparing hip fracture subjects with elderly non-fracture subjects) presented in Table 7 indicates that the area under the ROC curve ("AUC") is 0.63 (95% CI: 0.61-0.79) and the fracture odds ratio is 2.16 (95% CI: 1.46-3.19). The age- and BMI-adjusted AUC is 0.79 (95% CI: 0.73-0.84) and the age-adjusted odds ratio is 1.75 (95% CI: 1.15-2.65).

Table 7: SOS Fracture Discrimination - Area Under ROC Curve and Odds Ratio Study 201

BMI & Age adjusted			**BMI adjusted**		
ROC (95% CI)	Odds ratio (95% CI)	p-value	ROC (95% CI)	Odds ratio (95% CI)	p-value
0.79 (0.73-0.84)	1.92 (1.22-3.02)	0.005	0.77 (0.70-0.83)	2.29 (1.49-3.54)	0.0002
Age adjusted			**Unadjusted**		
ROC (95% CI)	Odds ratio (95% CI)	p value	ROC (95% CI)	Odds ratio (95% CI)	p value
0.75 (0.66-0.84)	1.75 (1.15-2.65)	0.009	0.69 (0.61-0.79)	2.16 (1.46-3.19)	0.0001

Table 8 shows the results of a logistic regression with fracture status as the dependent variable (excluding young healthy subjects) and SOS as the independent variable, adjusting for age and BMI. This analysis shows that for every 100 m/sec decrease in SOS the odds of fracture increase by about 50% and that for every decrease of 162 m/sec in SOS the odds of fracture double. Age and BMI are independent predictors of fracture risk: for every additional decade of age the risk of fracture increases by nearly 2.5 times, and for every decrease of one kg/m^2 in BMI, the risk of fracture increases by more than 25%.

Table 8: Results of Multivariate Logistic Regression - Study 201

Variable	Parameter Estimate	Standard Error	Chi-Square	p-value
Intercept	-14.96	7.53	3.95	0.05
Age	-0.09	0.04	6.72	0.01
BMI	0.23	0.06	14.27	0.0002
SOS	0.004	0.0015	7.94	0.005

No adverse events of any kind were reported in the course of this clinical study.

Conclusions: This case-control based study has shown that the Omnisense can significantly discriminate between young and healthy subjects, who are at very low risk of any osteoporotic fracture, and a group of elderly subjects, who are known to be, on the average, at high risk of fracture. Moreover, the Omnisense was also found to significantly discriminate between osteoporotic hip fracture subjects and age-matched elderly non-fracture subjects. This finding is noted despite a high likelihood that there are a significant number of osteoporotic subjects in the non-fracture group. The odds ratios found in this study, which can be considered fracture risk estimates, are comparable to those of other bone assessment devices.

These study results show that the SOS, as measured by the Omnisense, can be considered as an important factor in aiding the physician when diagnosing a patient for osteoporosis and determining the patient's risk of fracture.

2. ASSESSMENT OF HIP, WRIST AND VERTEBRAL FRACTURE RISK (STUDY 202)

Study design and subject population: The objective of Study 202 was to determine the ability of Omnisense SOS measurements to discriminate osteoporotic hip, vertebral, and wrist fracture subjects from non-fracture subjects, and to determine the fracture risk estimate. Thus, four groups of subjects were enrolled and found eligible to be analyzed in the study: 94 hip fracture subjects (HF), 50 vertebral fracture subjects (VF), 41 wrist fracture subjects (WF), and 89 elderly non-fracture subjects (NF). All subjects were in the age range of 55 to 85. The study was was conducted by one investigator at Rambam Medical Center, Haifa, Israel.

Results: As seen in Table 9, hip fracture subjects had a mean SOS of 3873±154 m/s, vertebral fracture subjects had a mean SOS of 3877±144 m/s, wrist fracture subjects had a mean SOS of 3880±154 m/s, and non-fracture subjects had a mean SOS of 3953±138 m/s. All fracture subjects had a mean SOS of 3878±154. All of the differences between the mean SOS of each of the fracture group and the mean SOS of the non-fracture group were statistically significant ($p<0.01$). The SOS distributions for the study groups are illustrated in Figure 3. While there is a clear difference in the SOS distributions between the fracture groups and the non-fracture group, there is considerable overlap as well in the range of 3800-3900 m/sec.

Table 9: SOS Measurements by Study Group - Study 202

Speed of Sound (m/sec)	Hip Fracture n (%)	Vertebral Fracture n (%)	Wrist Fracture n (%)	All Fracture n (%)	Elderly Non-Fracture n (%)
<3800	32 (34.0)	16 (32.0)	14 (34.1)	51 (32.1)	15 (16.9)
3800-3899	21 (22.3)	8 (16.0)	7 (17.1)	32 (20.1)	21 (23.6)
3900-3999	20 (21.3)	16 (32.0)	10 (24.4)	42 (26.4)	22 (24.7)
4000-4099	16 (17.0)	7 (14.0)	8 (19.5)	24 (15.1)	16 (18.0)
4100-4199	4 (4.3)	3 (6.0)	1 (2.4)	8 (5.0)	12 (13.5)
4200-4299	1 (1.1)	0 (0.0)	1 (2.4)	2 (1.3)	2 (2.2)
4300+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Total	**94 (100.0)**	**50 (100.0)**	**41 (100.0)**	**159 (100.0)**	**89 (100.0)**
Mean±SD	**3873±154**	**3877±144**	**3880±154**	**3878±154**	**3953±138**
Range	**3326-4246**	**3577-4149**	**3415-4206**	**3326-4246**	**3718-4325**
T-test p-value (compared to non-fracture)	**<0.0001**	**0.003**	**0.01**	**0.0001**	**----**

Figure 3: SOS Distribution by Study Group - Study 202

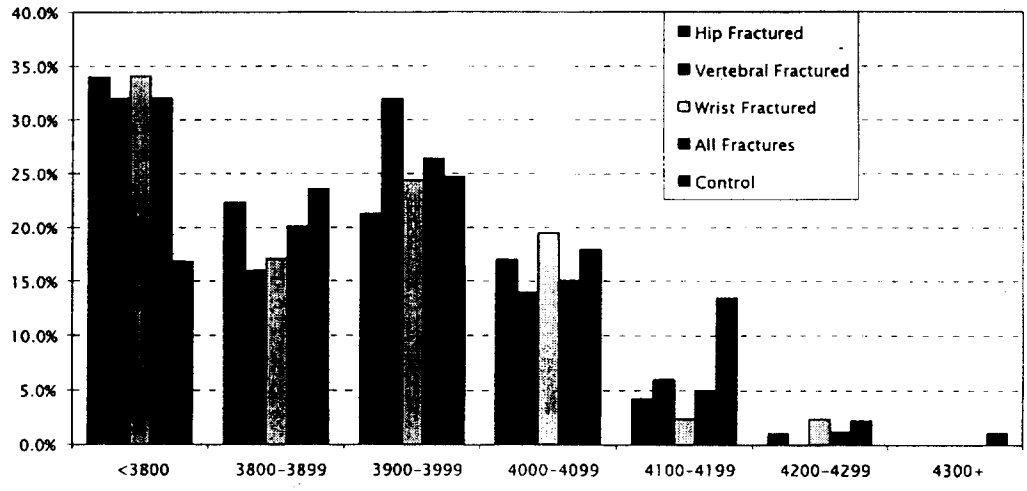

Table 10 shows the distribution of SOS T-scores for each of the fracture groups and the non-fracture subjects. Among the different fracture groups: 60% of the hip fracture subjects, 52% of the vertebral fracture subjects and 54% of the wrist fracture subjects had T-scores less than –2.5, as did 46% of non-fracture subjects. Conversely, less than 10% of each of the fracture groups had T-scores greater than -1.0, while 24% of non-fracture subjects had T-scores greater than -1.0.

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Table 10: SOS Measurement T-Scores by Study Group - Study 202

T-Score	Hip Fracture n (%)	Vertebral Fracture n (%)	Wrist Fracture n (%)	All Fracture n (%)	Elderly Non-Fracture n (%)
< -2.5	56 (59.6)	26 (52.0)	22 (53.6)	87 (54.7)	41 (46.0)
-2.5 to 1.0	31 (33.0)	20 (40.0)	16 (39.0)	59 (37.1)	27 (30.3)
> 1	7 (7.4)	4 (8.0)	3 (7.4)	13 (8.2)	21 (23.6)
Total	**94 (100.0)**	**50 (100.0)**	**41 (100.0)**	**159 (100.0)**	**89 (100.0)**
Mean±SD	**-3.03±1.55**	**-2.99±1.45**	**-2.96±1.56**	**-2.98±1.55**	**-2.22±1.39**
Range	**-8.56 to 0.74**	**-6.02 to -0.24**	**-7.66 to 0.33**	**-8.56 to 0.74**	**-4.60 to 1.54**

The logistic regression analysis for fracture discrimination (*i.e.*, comparing all fracture subjects with elderly non-fracture subjects) presented in Figure 11 indicates that the area under the ROC curve ("AUC") is 0.63 (95% CI: 0.56-0.70) and the fracture odds ratio is 1.72 (95% CI: 1.29-2.30). The age- and BMI-adjusted AUC is 0.70 (95% CI: 0.63-0.77) and the age-adjusted odds ratio is 1.41 (95% CI: 1.04-1.93).

Table 11: SOS Fracture Discrimination Area Under ROC Curve and Odds Ratio - Study 202

BMI & Age adjusted			**BMI adjusted**		
ROC (95% CI)	**Odds ratio (95% CI)**	**p-value**	**ROC (95% CI)**	**Odds ratio (95% CI)**	**p-value**
0.70 (0.63-0.77)	1.43 (1.04-1.95)	0.03	0.63 (0.56-0.70)	1.74 (1.29-2.33)	0.0002
Age adjusted			**No adjustment**		
ROC (95% CI)	**Odds ratio (95% CI)**	**p-value**	**ROC (95% CI)**	**Odds ratio (95% CI)**	**p-value**
0.70 (0.63-0.77)	1.41 (1.04-1.93)	0.03	0.63 (0.56-0.70)	1.72 (1.29-2.30)	0.0003

Table 12 shows the results of a logistic regression with fracture status as the dependent variable and SOS as the independent variable, adjusting for age and BMI. This analysis shows that the odds of hip, vertebral, wrist or any fracture increase by 50% for a decrease in SOS of 241 m/sec, 127 m/sec, 142 m/sec and 174 m/sec respectively. Furthermore the odds of hip, vertebral, wrist or any fracture double when the SOS decreases by 412 m/sec, 217 m/sec, 242 m/sec and 297 m/sec, respectively.

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Table 12: Results of Multivariate Logistic Regression

Variable	Parameter Estimate	Standard Error	Chi-Square	p-value
Intercept	-3.11	4.72	0.43	0.51
Age	-0.09	0.02	16.67	0.0001
BMI	-0.02	0.04	0.19	0.66
SOS	0.0023	0.0011	4.91	0.03

No adverse events of any kind were reported in the course of this clinical study.

Conclusions: This case-control based study has shown that the Omnisense can significantly discriminate between subjects having any of the most common osteoporotic fractures (*i.e.*, hip, vertebral and wrist fractures) and age matched non-fracture controls, even though the control group, being also formed of elderly subjects, is likely comprised of a significant number of osteoporotic subjects. A significant discrimination was similarly observed between each of the fracture subjects grouped according to their type of osteoporotic fracture, and the control group. The odds ratios found in this study, which can be considered fracture risk estimates, are comparable to those found in Study 201, and also to those of other bone assessment devices.

These study results confirm once again, while widening the spectrum of the type of fractures, that the SOS as measured by the Omnisense can be used by physicians when diagnosing a patient for osteoporosis and determining the patient's risk of fracture.

3. COMBINED CROSS-SECTIONAL STUDIES

The 201 and 202 cross-sectional studies were very similar in many respects. Both studies had similar patient populations and recruited hip fracture subjects and healthy non-fracture subjects in the same age groups. Since hip fracture is the most important osteoporotic fracture from a personal, public health and economic point of view, it is important to obtain estimates of Omnisense hip fracture discrimination ability that are as accurate as possible. To this end, the hip fracture and healthy non-fracture groups in these two studies have been pooled in order to arrive at a more precise estimate of the Omnisense capabilities.

The combined hip fracture group consists of 144 subjects, 50 from Study 201 and 94 from Study 202. The combined non-fracture group consists of 219 subjects, 130 from Study 201 and 89 from Study 202.

Results: Table 13 shows the distribution of SOS measurements for the combined hip fracture group and the combined non-fracture group. Hip fracture subjects had a mean SOS of 3869±152 m/sec, while non-fracture subjects had a mean SOS of 3960±142 m/sec ($p<0.0001$). As seen in this table, there is considerable overlap between the two groups in the range of 3800-4000 m/sec, since elderly subjects in the non-fracture group might also be osteoporotic.

Table 13: SOS Measurements by Study Group - Pooled Study 201+202

Speed of Sound (m/sec)	Hip Fracture n (%)	Elderly Non-Fracture n (%)	p-value
<3600	3 (2.8)	2 (0.9)	
3600–3699	10 (6.9)	0 (0.0)	
3700-3799	37 (25.7)	28 (12.8)	
3800-3899	33 (22.7)	51 (23.3)	
3900-3999	31 (21.5)	59 (26.9)	
4000-4099	21 (14.6)	38 (17.3)	
4100-4199	8 (5.6)	30 (13.7)	
4200-4299	1 (0.7)	9 (4.1)	
4300+	0 (0.0)	2 (0.9)	
Total	**144 (100.0)**	**219 (100.0)**	
Mean±SD	**3869±152**	**3960±142**	**<0.0001**
Range	**3326 - 4246**	**3582 - 4359**	

Table 14 shows the distribution of SOS T-scores for the combined group of hip fracture subjects, as well as the combined group of non-fracture subjects. Among hip fracture subjects, 63% had T-scores less than -2.5, while 42% of non-fracture subjects had T-scores less than -2.5. Conversely, 8% of hip fracture subjects had T-scores greater than –1.0, while 24% of non-fracture subjects had T-scores greater than –1.0.

Table 14: SOS Measurement T-Scores by Study Group - Pooled Study 201+202

T-Score	Hip Fracture n (%)	Elderly Non-Fracture n (%)
< -2.5	91 (63.2)	92 (42.0)
-2.5 to -1.0	41 (28.5)	75 (34.2)
> -1.0	12 (8.3)	52 (23.7)
Total	**144 (100.0)**	**219 (100.0)**
Range	**-8.56 to 0.10**	**-5.97 to 1.96**

The logistic regression analysis for hip fracture discrimination (*i.e.*, comparing hip fracture subjects with elderly non-fracture subjects) presented in Table 15 indicates that the area under the ROC curve ("AUC") is 0.67 (95% CI: 0.61-0.73) and the fracture odds ratio is 1.95 (95% CI: 1.53-2.49). The age- and BMI-adjusted AUC is 0.76 (95% CI: 0.70-0.82) and the age-adjusted odds ratio is 1.54 (95% CI: 1.18-2.00).

Table 15: SOS Fracture Discrimination Area Under ROC Curve and Odds Ratio Pooled Study 201+202 Age Range 55-85

BMI & Age adjusted			**BMI adjusted**		
ROC (95% CI)	Odds ratio (95% CI)	p-value	ROC (95% CI)	Odds ratio (95% CI)	p-value
0.76 (0.70-0.82)	1.50 (1.15-1.96)	0.003	0.70 (0.64-0.76)	1.91 (1.49 – 2.46)	0.0001
Age adjusted			**Unadjusted**		
ROC (95% CI)	Odds ratio (95% CI)	p-value	ROC (95% CI)	Odds ratio (95% CI)	p-value
0.75 (0.70-0.81)	1.54 (1.18-2.00)	0.001	0.67 (0.61-0.73)	1.95 (1.53-2.49)	0.0001

Table 16 shows the results of a multivariate logistic regression with fracture status as the dependent variable and SOS as the independent variable, adjusting for age and BMI. This analysis shows that for every 135 m/sec decrease in SOS the odds of fracture increase by about 50% and that for every decrease of 231 m/sec in SOS the odds of fracture doubles.

Table 16: Results of Multivariate Logistic Regression

Variable	Parameter Estimate	Standard Error	Chi-Square	p-value
Intercept	-4.79	4.27	1.26	0.26
Age	-0.11	0.02	29.6	<0.0001
BMI	0.12	0.04	10.3	0.001
SOS	0.0027	0.0009	8.68	0.003

Conclusions: The results from combining the two fracture studies show that the Omnisense can significantly discriminate between osteoporotic hip fracture subjects and age-matched non-fracture subjects even after controlling for age and BMI. The odds ratios found in this analysis are comparable to those of other bone assessment devices.

4. PRECISION STUDY

The objective of this study was to determine the precision of the Omnisense, as measured by the coefficient of variation ("CV"). The distal one-third radius SOS of each subject was measured twice by three different operators. Probes were repositioned between each measurement. The CV was calculated using the SAS ANOVA procedure, which reports the overall mean, the mean square error (using subject-operator combination as a blocking factor) and the coefficient of variation (the mean square error divided by the mean). The CV was reported for all measurements, as well as stratified by operator and by menopausal status. The variance of each CV was also calculated so that 95% confidence intervals could be reported. Fifteen subjects were measured, 10 premenopausal women and 5 postmenopausal women.

A total of 45 pairs (15 subjects times 3 operators) of SOS measurements were used to compute the CVs. The overall CV was 0.40% (95% CI: 0.39% to 0.41%). For pre-menopausal women the CV was 0.29% and for postmenopausal women the CV was 0.57%.

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A total of six different operators performed SOS measurements in this study. Their CVs ranged from 0.27% to 0.66%.

The coefficient of variation can also be calculated in two different "standardized CV" forms, SCV_1 and SCV_2. SCV_1 is computed by dividing the measured mean square error by 95% of the individual range, which is taken from the North America Normative Database (Section 3.10.1.1 above). SCV_1 was found to be 1.8%. SCV_2 is computed by dividing the mean square error by the difference of the young healthy mean SOS (taken from the North America Normative Database, section 3.10.1.1) and that of the osteoporotic fracture mean SOS (the mean of the "All Fracture" group in the 202 Study, section 3.10.2.2). SCV_2 is higher than SCV_1, and equals 5.9%.

No adverse events of any kind were reported in the course of this clinical study.

Conclusions: The *in vivo* precision of the Omnisense, as measured by the coefficient of variation, is 0.40%. There were some relative differences in CV between premenopausal and postmenopausal subjects. Differences in precision between premenopausal subjects and postmenopausal subjects have been found in DXA measurements (postmenopausal CV higher than premenopausal CV) as well as in QUS measurements of the calcaneus (postmenopausal CV lower than premenopausal CV). There were also differences between CVs measured by different operators. Nevertheless, all CVs were well below 1%, indicating good precision for all subgroups, and thus allowing for a meaningful assessment of patient status relative to the reference range.

The mean square error, about 17m/sec, is similar in magnitude to the average change per year which is observed during the first years of sharp decline in SOS post menopause, as described in section 3.10.1 above. Thus, the Omnisense can provide precise estimates of bone status during this important time when bone changes are most pronounced.

XI. CONCLUSIONS DRAWN FROM STUDIES

A) RISK/BENEFIT ANALYSIS

The Sunlight Omnisense provides useful quantitative measurements of bone fragility via the velocity of acoustic ultrasound waves ("speed of sound" or "SOS") propagating along the distal one-third of the radius bone. The SOS data, when used in conjunction with other clinical risk factors, can aid physicians in the diagnosis of osteoporosis and other medical conditions leading to reduced bone strength and, ultimately, in the determination of fracture risk. The clinical effectiveness of the Omnisense compares to that or rivals that of established densitometry (BMD), but without exposure to ionizing radiation. Due to the low power levels used, the risks posed by the Omnisense are also signficantly lower than the already minimal risks posed by medical ultrasound devices used for other indications such as imaging. It is reasonable, therefore, to conclude that the benefits of the Omnisense outweigh the risk of illness or injury when used in accordance with the directions for use.

B) SAFETY

There were no complications, adverse events, or side effects reported for patients participating in the clinical studies investigating the Omnisense.

C) EFFECTIVENESS

Two Omnisense studies determined SOS values in a clinically normal population. Studies also demonstrated the ability of Omnisense SOS measurements to discriminate osteoporotic fracture subjects from age-matched non-fracture subjects, and young and healthy subjects, and thus to

enable determination of fracture risk estimates. A precision study also was conducted and demonstrated that the SOS measurements are reproducible.

XII. FDA DECISION

The applicant's manufacturing facility was inspected on August 25, 1999 and was found to be in compliance with the Quality System regulations. FDA issued an approval order on January 20, 2000.

XIII. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act(the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is futher restricted within the meaning of section 520(e)under the authority of section 515(d)(1)(B)(ii)insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Hazards to Health From Use of the Device. See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the attached labeling.

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